Review

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Current use of the faricimab in retinal diseases

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ABSTRACT

Faricimab, a novel drug in the field of ophthalmology, has garnered attention because of its promising applications in the treatment of various ocular conditions. This drug, with its dual targeting of angiopoietin-2 and vascular endothelial growth factor (VEGF), is a versatile intervention for the management of neovascular and inflammatory ocular disorders. Developed through meticulous research and clinical trials, faricimab holds promise as a multifaceted solution to longstanding challenges in ophthalmology. This review provides a comprehensive analysis of the current knowledge and clinical use of faricimab.

Keywords: Angiopoietin-2, dual mechanism, faricimab, ophthalmology, retina, vascular endothelial growth factor

INTRODUCTION

Faricimab, a groundbreaking pharmaceutical agent, has emerged as a focal point in ophthalmological therapeutics. As a novel drug, its development and mechanism of action represent a paradigm shift in addressing various ocular conditions. Faricimab is a bispecific monoclonal antibody designed to use intravitreally and faricimab does not only inhibits VEGF but also inhibits Angiopoietin-2. As we delve into the intricacies of faricimab's role in ophthalmology, it becomes evident that its introduction marks a pivotal juncture in the pursuit of more effective and patient-friendly treatments for ocular disorders. This review aims to navigate the current landscape, providing a comprehensive analysis of Faricimab's applications, supported by evidence from recent studies. The subsequent sections will expound on its clinical applications, shedding light on its impact on diverse ophthalmic conditions.

Angiopoietins, a family of growth factors involved in vascular stability, play pivotal roles in angiogenesis. In adults, the Ang/Tie pathway is mainly responsible for the regulation of vascular homeostasis, modulation of vascular permeability, and neoangiogenic and proinflammatory processes.[1,2] Tie-2 is a transmembrane receptor that is especially found in the endothelial cells of blood vessels, and Ang-1 and Ang-2 compete with each other to bind Tie-2. In addition, the binding of either Ang-1 or Ang-2 has different effects on the Tie-2 pathway. Studies have shown that when Ang-1 binds to Tie-2, causing phosphorylation of the receptor and may promote vessel maturation, endothelial cell migration, and initiating its effects of inhibit vascular permeability, it also preserves vascular stability. Ang-1 promotes vascular stabilization and maturation, whereas Ang-2 serves as a dynamic modulator, exerting context-dependent effects on vessel formation. Ang-2 may disrupt the connections between endothelial cells and promote vascular regression, and Ang-2 may promote vascular angiogenesis.[2] Ang-2 has emerged as a key molecular player in ophthalmology. Dysregulation of angiopoietin expression is often implicated in neovascular ocular conditions such as age-related macular degeneration (AMD) and diabetic retinopathy. The intricate interplay between angiopoietins and vascular endothelial growth factor (VEGF) highlights their roles in the pathogenesis of these disorders.

DUAL MECHANISM OF FARICIMAB ACTION

Faricimab is an antibody engineered to simultaneously bind to and neutralise Angiopoietin-2 (Ang-2) and VEGF-A. Faricimab is an antibody that is engineered to be used intravitreally, designed with a dual mechanism targeting both Ang-2 and VEGF, which may improve the synergistic effects of these pathways. This unique approach positions faricimab as a promising therapeutic

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agent with the potential to address the complexity of neovascularization in ophthalmic pathologies. The integration of Ang-2 inhibition into ophthalmic therapeutics, as seen in faricimab, opens avenues for optimizing treatment regimens. By targeting multiple pathways with a single agent, there is a potential for extended dosing intervals, thereby alleviating the treatment burden on patients and clinics.

Ang-2, in its unbound state, acts as a context-dependent antagonist of Ang-1, promoting the destabilization of blood vessels and fostering conditions conducive to angiogenesis. By blocking Ang-2, Faricimab aims to mitigate this destabilizing influence, contributing to the stabilization of the vascular endothelium. This dual inhibition extends beyond Ang-2, as Faricimab also targets VEGF, a key mediator of angiogenesis and vascular permeability. The synergy between Ang-2 and VEGF inhibition offers more comprehensive control over pathological neovascularization, characteristic of conditions such as age-related macular degeneration (AMD) and diabetic retinopathy. By concurrently addressing two pivotal pathways, faricimab introduced the possibility of extended treatment intervals. This feature is particularly advantageous in reducing treatment burden for patients and optimizing the management of chronic ocular disorders.[1,2]

Clinical Studies with Faricimab in Age-Related Macular Degeneration

The AVENUE study was a phase 2 study of faricimab in treatment-naive nAMD patients, who were treated with five different regimens. The first-arm patients received ranibizumab (0.5 mg every four weeks. In the second arm, the patients received faricimab (1.5 mg every four weeks. In the third arm, the patients received faricimab (6.0 mg every four weeks. In the fourth arm, patients received faricimab, 6.0 mg every 4 weeks until week 12) followed by faricimab, 6.0 mg every 8 weeks). In the fifth arm, patients received ranibizumab 0.5 mg every 4 weeks until week 8, followed by faricimab, 6.0 mg every 4 weeks). Avenue results didn't show statistically significant differences in BCVA and anatomical outcomes between the faricimab arms and the monthly ranibizumab control arm week 36.[3]

The STAIRWAY study was a phase 2 study of faricimab in nAMD patients over 56 weeks. Participants received either 4 monthly 6 mg faricimab as a loading dose and received 6 mg faricimab every 12 or 16 weeks, or 0.5 mg ranibizumab every 4 weeks. The primary endpoint was the change in BCVA at week 40 of the study. The results showed that faricimab administered at 12- and 16-week intervals maintained visual acuity and improved anatomical parameters observed in macular OCT not inferiorly to ranibizumab administered every month.[4]

The TENAYA and LUCERNE trials are pivotal Phase III studies evaluating the efficacy and safety of Faricimab in AMD. These multicenter, randomized, double-masked controlled trials have provided comprehensive insights into the performance of drugs compared to the current standards of care. The primary endpoints included visual acuity, anatomical changes in retinal morphology, and safety profiles. Results from the Tenaya and Lucerne trials demonstrated promising achievements in the primary endpoints. Faricimab was administered monthly for 4 months as loading doses to patients assigned to one of the eight, 12, or 16 weekly dosing groups according to anatomical and visual outcomes. After week 60, the patients' treatment intervals could be extended through a treat-and-extend personalized treatment interval (PTI). Faricimab has shown non-inferiority to aflibercept and met the primary endpoint of clinical trials. The primary endpoint was the mean change in best-corrected visual acuity (BCVA) in the ETDRS from baseline to weeks 40, 44, and 48. These trials showed impressive durability data in patients randomized to receive faricimab. By week 48, nearly 80% of the faricimab-treated patients had a dosing interval of at least 12-week dosing interval. In detail, percentage of patients treated with faricimab with 12-week dosing interval was 34% in TENAYA and 32.9% in LUCERNE; and with 16-week dosing interval was 45.7% in TENAYA and 44.9% in LUCERNE. Approximately 21% of the faricimab-treated patients remained at 8-week intervals. Mean BCVA change from baseline with faricimab was +5.1 and +6.6 letters and with aflibercept +5.1 and +7.8 letters, Tenaya and Lucerne, respectively. The mean change in the central subfoveal thickness (CST) was similar between the treatment groups. For faricimab mean change over weeks 40, 44 and 48 was −136.8 µm in Tenaya and −137.1 µm in Lucerne and for aflibercept treated patients mean change over the same weeks was −129.4 µm in Tenaya and −130.8 µm in Lucerne. The rate of serious ocular adverse events was similar between aflibercept and faricimab, with no evidence of occlusive retinal vasculitis. These findings underscore its potential as a robust treatment option for AMD.[5]

One of the distinguishing features of faricimab is its potential for extended dosing intervals. Clinical studies have explored the feasibility of administering faricimab less frequently than traditional anti-VEGF agents while maintaining therapeutic efficacy. Through week 48, nearly 78% of the patients received injections at least 12 weekly intervals after loading doses. Detailed assessments of anatomical changes, such as reduction in central retinal thickness and improvement in macular morphology, were performed. The changes in CST in

both treatment arms were similar and comparable. The safety profile of faricimab has been the focus of rigorous examination in clinical trials. Analysis of adverse events, ocular and systemic safety parameters, and the incidence of treatment-related complications has provided valuable data to ensure the drug's overall safety and tolerability.[5]

Clinical Studies with Faricimab in Diabetic Retinopathy and Diabetic Macular Edema

The BOULEVARD study was a phase 2 study of faricimab in patients with DME. Patients previously untreated with anti-VEGF agents received 1.5 mg or 6 mg faricimab and 0.3 mg ranibizumab, while non-treatment-naive patients received 6 mg faricimab and 0.3 mg ranibizumab. All groups were injected monthly for the first 20 weeks, and patients were followed up for 16 weeks. In the treatment-naive group, the mean change in faricimab 6 mg treated patients +13.9 letters and +11.7 letters in the 1.5 mg faricimab group. The mean change in the ranibizumab-treated group was +10.3 letter. In both treatment-naive and non-treatment naive patients, a more marked improvement in anatomical parameters and DRSS scores in faricimab regimens was noted compared to the aflibercept arm.[6]

The YOSEMITE and RHINE trials are pivotal Phase III studies evaluating the impact of faricimab on diabetic retinopathy and diabetic macular edema. Clinical studies have systematically assessed Faricimab's efficacy in managing diabetic macular edema, focusing on parameters such as visual improvement and prevention of disease progression.[7] Yosemite and Rhine trials met its primary endpoint. The mean BCVA change for patients who are receiving faricimab is +11.6 and +10.8 ETDRS letters, and +10.1 and 10.3 ETDRS letters for aflibercept patients, Yosemite and Rhine, respectively. The effect of faricimab on diabetic macular edema has been investigated in terms of anatomical changes in central retinal thickness and fluid accumulation. Improvements in CST were significantly greater in faricimab-treated patients than in aflibercept-treated patients after 12 months of treatment. In Yosemite, mean CRT reductions from baseline −196·5 μm (−204·7 to −188·4) in the faricimab PTI and −170.3 μm (−178.5 to −162·2) in the aflibercept groups, and in Rhine, mean CST reductions from baseline −187·6 μm (−195·8 to −179·5) in the faricimab and −170·1 μm (−178·3 to −161·8) in the aflibercept groups. In the PTI Faricimab arm 52.8% in Yosemite and 51% in Rhine achieved 16-week dosing at year 1 year.[7]

Clinical Studies with Faricimab in Macular Edema with Branch and Central Retinal Vascular Occlusion

BALATON and COMINO are randomized, double-blind studies that evaluate the efficacy, safety, and pharmacokinetics of faricimab compared to aflibercept in patients with macular edema secondary to retinal vein occlusion. The Balaton and Comino trials represent significant Phase III clinical studies specifically designed to assess the impact of faricimab on macular edema associated with branch retinal vascular disease. For the first 20 weeks, the patients were randomly assigned 1:1 to receive six monthly injections of either faricimab or aflibercept. From weeks 24 to 72, all patients received faricimab up to every 16 weeks according to a personalized treatment interval dosing based on treat and extend regimen.[8]

The BALATON study was conducted on patients with branch retinal vein occlusion, whereas the COMINO study was conducted on patients with central retinal or hemiretinal vein occlusion. The primary endpoint of each study was the change in best-corrected visual acuity (BCVA) from baseline to 24 weeks. Both studies met the primary end points. Faricimab showed non-inferior visual acuity gains compared to aflibercept. The mean vision gains from baseline in the BALATON were +16.9 EDTRS letters in the faricimab arm, and +17.5, letters in the aflibercept arm at 24 weeks. In the COMINO trial, vision gains were +16.9 letters in, faricimab arm and +17.3 letters in the aflibercept arm at 24 weeks. CST improvements were similar across studies. In the BALATON trial, the improvements were −311.4 μm in the faricimab arm and −304.4 μm in the aflibercept arm. In the COMINO trial, the improvements were −461.6 μm for faricimab and −448.8 μm for the aflibercept arm.

CONCLUSION

In the field of ophthalmology, the exploration of faricimab has unfolded as a narrative of its transformative potential, offering a multifaceted solution to various ocular disorders. The distinctive mechanism of dual inhibition by faricimab, which targets both angiopoietin-2 and vascular endothelial growth factor, represents a paradigm shift in ophthalmic therapeutics. This innovative approach addresses the complexity of angiogenesis and vascular regulation, offering a comprehensive solution for the pathological processes in various ocular disorders. Considering age-related macular degeneration, diabetic macular edema, or macular edema secondary to retinal vein occlusion, faricimab consistently demonstrates its potential to improve visual outcomes, stabilize retinal morphology, and potentially reduce the treatment burden through extended dosing intervals. Intravitreal faricimab minimally improved vision even in eyes with treatment-resistant neovascular AMD. In addition, longer dosing intervals have advantages over ranibizumab or aflibercept.[9] Regarding toxicity, intraocular events are

present; however, there seem to be fewer instances of serious inflammatory events observed with the use of faricimab when compared to the toxicities associated with brolucizumab.[10] Faricimab's adaptability caters to the nuances of individual patient profiles, optimizes therapeutic interventions, and potentially enhances patient compliance. Beyond controlled trials, real-world evidence studies and long-term follow-up investigations will provide valuable insights into the practical applicability of faricimab.

ETHICAL DECLARATIONS

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